Intraductal carcinoma of the prostate is not a diagnostic entity

Delahunt, Brett ; Egevad, Lars ; Samaratunga, Hemamali ; Srigley, John R ; Cheng, Liang ; Clouston, David ; Furusato, Bungo ; Kench, James ; Leite, Katia R M ; MacLennan, Gregory T ; Moch, Holger ; Pan, Chin-Chen ; Ro, Jae ; Tsuzuki, Toyonori ; van der Kwast, Theodorus ; Wheeler, Thomas ; Yaxley, John W

Abstract: We have read with interest the recent debate between Drs Varma and Epstein regarding the grading of intraductal carcinoma of the prostate.[1] Unfortunately, the arguments as presented do little to abate the confusion surrounding this so-called diagnostic entity.

DOI: https://doi.org/10.1111/his.14260

PROFESSOR BRETT DELAHUNT (Orcid ID : 0000-0002-5398-0300)
PROFESSOR LARS EGEVAD (Orcid ID : 0000-0001-8531-222X)
DR LIANG CHENG (Orcid ID : 0000-0001-6049-5293)
PROFESSOR CHIN-CHEN PAN (Orcid ID : 0000-0001-9990-8972)

Article type : Correspondence

Intraductal carcinoma of the prostate is not a diagnostic entity

Brett Delahunt[1], Lars Egevad[2], Hemamali Samaratunga[13], John R Srigley[4], Liang Cheng[5], David Clouston[6], Bungo Furusato[7], James Kench[8], Katia R M Leite[9], Gregory T MacLennan[10], Holger Moch[11], Chin-Chen Pan[12], Jae Ro[13], Toyonori Tsuzuki[14], Theodorus van der Kwast[15],Thomas Wheeler[16], John W Yaxley[17].

[1] *Department of Pathology and Molecular Medicine, Wellinton School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand; Email: brett.delahunt@otago.ac.nz*

[2] *Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden; Email: Lars.Egevad@ki.se*

[3] *Aquesta Uropathology and University of Queensland, Brisbane, Queensland, Australia; Email: Hema@aquesta.com.au*

[4] *Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada; Email: john.srigley@thp.ca*

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/HIS.14260

[5] *Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN; Email: lcheng@iupui.edu*

[6] *TissuPath, Mount Waverley, Vic, Australia; Email: david.clouston@tissupath.com.au*

[7] *Department of Pathology, Nagasaki University Graduate School of Biomedical Sciences and Cancer Genomics Unit, Clinical Genomics Center, Nagasaki University Hospital, Sakamoto, Nagasaki, Japan; Email: befurusato@me.com*

[8] *Department of Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital and Central Clinical School, University of Sydney, Sydney, NSW, Australia; Email: James.Kench@health.nsw.gov.au*

[9] *Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, Brazil; Email: katiaramos@usp.br*

[10] *Department of Pathology and Urology, Case Western Reserve University, University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA; Email: Gregory.MacLennan@UHhospitals.org*

[11] *University and University Hospital Zurich, Department of Pathology and Molecular Pathology, Zurich, Switzerland; Email: holger.moch@usz.ch*

[12] *Department of Pathology, Taipei Veterans General Hospital, Taipei, Taiwan; Email: chinchenpan@gmail.com*

[13] *Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Weill Medical College of Cornell University, Houston, Texas, USA; Email: JaeRo@houstonmethodist.org*

[14] *Department of Surgical Pathology, Aichi Medical University, School of Medicine, Nagakute, Japan; Email: tsuzuki.toyonori@gmail.com*

[15] *Department of Pathology, Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada; Email: Theodorus.vanderKwast@uhn.ca*

[16] *Department of Pathology and Laboratory Medicine, Baylor St. Luke's Medical Center and Department of Pathology & Immunology, Baylor College of Medicine, Houston, Texas, USA; Email: twheeler@bcm.edu*

[17] *Department of Medicine, University of Queensland, Wesley Urology Clinic, Royal Brisbane and Women's Hospital, Brisbane, Australia; Email: john@wesleyurologyclinic.com.au*

Key words: Prostate; carcinoma; intraductal carcinoma of prostate; International Society of Urological Pathology; prognosis

Author for correspondence and reprints:
Professor Brett Delahunt, Department of Pathology and Molecular Medicine, Wellington School of Medicine and Health Sciences, University of Otago – Wellington, 23a Mein Street, Wellington, New Zealand.
Facsimile: +64 4 385 5930
Telephone +64 4 385 5575
E-mail: brett.delahunt@otago.ac.nz

The authors have no conflicts of interest to declare

We have read with interest the recent debate between Drs Varma and Epstein regarding the grading of intraductal carcinoma of the prostate.[1] Unfortunately, the arguments as presented do little to abate the confusion surrounding this so-called diagnostic entity.

We disagree with the definition of IDCP as provided in the introduction.[1] IDCP is marked by the presence of malignant, not atypical cells, in pre-existing prostatic ducts, as the latter can apply to high grade prostatic intraepithelial neoplasia and so-called atypical intraductal proliferation.

As described IDCP is simply as its name suggests – infiltration of ducts by aggressive carcinoma and is therefore analogous to intravascular or lymphatic invasion by tumour. The designation IDCP is unfortunate as it has some similarities to ductal carcinoma *in situ* of the breast, which as the terminology clearly states, is a non-invasive lesion.

Studies have appeared identifying IDCP as an *in situ* lesion in the absence of invasive malignancy and much of the debate regarding the validity of grading IDCP surrounds the existence of this entity. In the reports relating to so-called *in situ* IDCP there are concerns relating to completeness of sampling of the specimens.[2] Two studies, where it is claimed that there was complete sampling of radical prostatectomy specimens, relate to 5 cases of i*n situ* IDCP (or

perhaps 3 cases as it is uncertain if the cases reported in the latter study were the same as those in the initial report).[3,4] Interestingly these cases are all from one institution and it is surprising that, if IDCP is a precursor lesion, many other cases have not been discovered. Despite this it has been stated in the Bluebook that IDCP is found without invasive carcinoma in approximately 10% of radical prostatectomy specimens following (the detection of) pure IDCP on biopsy. These observations are based upon a sample of only 21 cases[3] and do not accord with our collective experience.

In one of the studies noted above, the molecular genetics of i*n situ* IDCP was investigated and, while the results were very incomplete, it was shown that the features were similar to those of high grade invasive cancer.[4] These results were interpreted to imply that *in situ* IDCP was an aggressive tumour. It would be equally valid to imply that the results confirmed that the tumour foci were, in fact, invasive carcinoma that had invaded a duct.

We would take issue with the claim that it is spurious that historical studies incorporated IDCP into grading of prostate cancer. Clearly this is not true, as IDCP was not recognized by the authors of many of the earlier studies, including Gleason himself. In the WHO Bluebook it is noted that IDCP may be found in 17% of prostatectomies.[5] An important observation in relation to this is that the majority of comedonecrosis seen in prostatic adenocarcinoma is IDCP,[6] and as such it is apparent that many cases of high grade tumour would be under-graded if IDCP was not incorporated. This is particularly relevant if the recommendation to severely limit immunohistochemical staining for basal cells is followed.

It has been suggested that to include IDCP in the grading of otherwise low grade cancer would have a significant effect on patient management and in some circumstances patients could be candidates for active surveillance. This is in direct contradiction of the findings of a survey involving a group of urological pathologists.[7] In the survey it was agreed that IDCP was an independent driver of prognosis and a major contraindication for active surveillance. We would concur with this latter recommendation, as IDCP is simply an invasive high grade cancer and should be treated and graded as such, with appropriate reporting of tumour volume and of

the percentage of pattern 4 and 5 tumour present. Surely, if IDCP is included in the dimensions of the tumour, confers an adverse prognosis and excludes patients from conservative management,[7] the logical course would be to include it in the final grade which would have the same treatment and prognostic implications.

In an international consensus report, authored by 31 prostate cancer experts which lays out a detailed argument against the recommendation that IDCP not be graded, it was acknowledged that IDCP is an aggressive duct invasive tumour that should be reported, graded and treated as such.[2] It was also noted that the lack of consistency in diagnostic criteria has contributed to confusion regarding the nature of IDCP as there is overlap with the features of prostatic intraepithelial neoplasia.[2] We contend that if IDCP is present it should be included in the tumour grade. If the features do not permit definitive assessment then the lesion should be reported as atypical intraductal proliferation and a repeat biopsy recommended.

References

1. Varma M, Epstein JI. Head to head: should intraductal component of invasive prostate cancer be graded? Histopathology in press.

2. Samaratunga H, Delahunt B, Egevad L, et al. Intraductal carcinoma of the prostate is an aggressive form of invasive carcinoma and should be graded. *Pathology* 2020;52;192-196.

3. Robinson BD, Epstein JI. Intraductal carcinoma of the prostate without invasive carcinoma on needle biopsy. Emphasis on radical prostatectomy findings. *J Urol.* 2010;184:1328-1333.

4. Kahni F, Wobker SE, Hicks JL et al. Intraductal carcinoma of the prostate in the absence of high grade invasive carcinoma represents a molecularly distinct type of in situ carcinoma enriched with oncogenic driver mutations. *J Pathol.* 2019;249:79-89.

5. Moch H, Humphrey PA, Ulbright TM, Reuter VE editors. . *WHO Classification of tumours of the Urinary System and male genital organs.* Lyon: IARC Press; 2016.

6. Fine SW, Ai-Ahnadi HA, Chen YB, et al. Comedonecrosis revisited : strong association with intraductal carcinoma of the prostate. *Am J Surg Pathol.* 2018; 42:1036-41.

7. Gandhi JS, Smith S, Paner GP, et al. Reporting practices and resource utilization in the era of intraductal carcinoma of the prostate. A survey of genitourinary specialists. *Am J Surg Pathol.* 2020;44:673-680.

Acknowledgement

BD was the author of the letter and all co-authors contributed editorial revisions.